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  - ☐ Affidavits/declaration(s)
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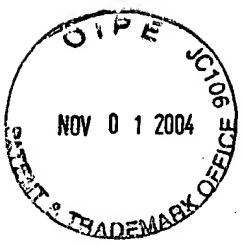

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On October 28, 2004

TOWNSEND and TOWNSEND and CREW LLP

By: Karen Kaslin

PATENT
Atty. Docket No.: 018512-000410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 3840
SILVIA and YU	Examiner: Bridget E. Bunner
Application No.: 09/623,304	Technology Center/Art Unit: 1647
Filed: February 21, 2001	APPELLANT'S BRIEF UNDER 37 C.F.R. 1.192
For: IDENTIFICATION AND EXPRESSION OF HUMAN KIR5.1	
Customer No.: 20350	

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Sir:

In response to the Office Communication mailed October 6, 2004, this brief is resubmitted to include reference to the specification by page and line numbers. This brief is filed in triplicate pursuant to 37 C.F.R. §1.192(a), following the Notice of Appeal, mailed December 15, 2003. No fee is believed to be due, however, payment of any necessary fee is authorized by charging to deposit account No. 20-1430.

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I. REAL PARTY IN INTEREST

The real party in interest in U.S. Application No. 09/623,304 is ICAgen, Inc.

II. RELATED APPEALS

Appellant is currently appealing the PTO's rejection of the claims in USSN 09/767,597, 09/548,933, and 09/927,267. The results of these appeals, which relate to the standard of assessing utility under 35 U.S.C. §101, will directly affect the decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-35 were originally filed. Claims 5 and 8-35 have been canceled. Claims 1-4, 6, and 7 are pending in the present application. In the Final Office Action mailed June 16, 2003, the Examiner rejected claims 1-4, 6, and 7 under 35 U.S.C. §101, alleging lack of a specific and substantial utility, even though the asserted utility was acknowledged by the Examiner as credible. The Examiner also rejected all pending claims under 35 U.S.C. §112, first paragraph, alleging failure to enable the claimed invention based on the utility rejection. Furthermore, the Examiner rejected the pending claims under 35 U.S.C. §112, second paragraph, for alleged indefiniteness.

IV. SUMMARY OF THE INVENTION

The invention relates to the first isolation and characterization of Kir5.1, an alpha subunit of inward rectifier potassium channels expressed in a variety of tissue and cell types. The instant application provides both the nucleotide and amino acid sequences of human Kir5.1 (SEQ ID NOs:1 and 2 beginning on page 64 of the specification), as well as methods of assaying for modulators of potassium channels comprising a Kir5.1 subunit (page 40, line 1, to page 44, line 20), antibodies for Kir5.1 (page 32, line 26, to page 34, line 18), and methods of detecting Kir5.1 nucleic acids and

polypeptides (page 7, lines 10-16, page 8, lines 15-19, and page 32, line 19, to page 39, line 29).

The pending claims are directed to an isolated nucleic acid encoding a polypeptide monomer comprising an alpha subunit of a potassium channel. The polypeptide monomer has the following attributes: (i) it forms, with at least one additional Kir alpha subunit, a potassium channel having the characteristic of inward rectification; and (ii) it is encoded by a nucleic acid that selectively hybridizes under highly stringent hybridization conditions to a nucleotide sequence of SEQ ID NO:2, wherein the stringent conditions comprise incubation at 42°C in a solution comprising 50% formamide, 5 x SSC, and 1% SDS or an incubation at 65°C in a solution comprising 5 x SSC and 1% SDS at 65°C with a wash in 0.2 x SSC and 0.1% SDS.

V. ISSUES ON APPEAL

1. The rejection for lack of utility is improper because the present invention meets the requirement under 35 U.S.C. §101 and the PTO patent examination guideline regarding utility by asserting utilities that are specific, substantial, and credible.

2. The rejection for lack of enablement is improper because the present invention does not lack utility.

3. The rejection for indefiniteness is further improper because the claims do particularly point out and distinctly claim the subject matter that Appellant regards as the invention according to the prevailing case law.

VI. CLAIM GROUPING

Claims 1-4, 6, and 7 do not stand and fall together. With regard to the indefiniteness rejection, claims 2-4, which are directed to an isolated nucleic acid that either encodes a human Kir5.1, a reference amino acid sequence (SEQ ID NO:1), or has a reference polynucleotide sequence (SEQ ID NO:2), can stand alone as they adequately

meet the requirement under 35 U.S.C. §112, second paragraph, even if claims 1, 6, and 7 are held indefinite.

VII. ARGUMENT

A. The Rejection for Lack of Utility Is Improper

Claims 1-4, 6, and 7 stand rejected under 35 U.S.C. §101 because the Examiner alleges that the claimed invention lacks either a well-established utility or a credible specific and substantial asserted utility.

Appellant respectfully traverses this rejection and argues that the rejection is improper. The present invention resides in the identification of Kir5.1 nucleic acids. Utility under 35 U.S.C. §101 is present because the identification of Kir5.1 nucleic acids permits one of skill in the art to screen for modulators, activators, or inhibitors of an inward rectifier potassium channel that comprises a Kir5.1 subunit, which can be used for treating, *e.g.*, hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency.

1. Standard to Assess Utility

According to MPEP §2107, the Examiner should review the claims and the supporting written description to determine whether the utility requirement under 35 U.S.C. §101 is met. No rejection based on lack of utility should be made if an invention has a well-established utility, *i.e.*, a utility that will be immediately appreciated by one of ordinary skill in the art based on the characteristics of the invention, regardless any such utility has been asserted. Neither should any rejection be made for lack of utility if an applicant has asserted a specific and substantial utility that would be considered credible by one of ordinary skill in the art.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. MPEP §2107.02 III A. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 183 USPQ 288, 297 (CCPA, 1974, emphasis in original). To overcome the presumption of sufficient utility as asserted by an applicant, the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility and provide a sufficient evidentiary basis for the conclusion. In other words, the Examiner "must do more than merely question operability--[he] must set forth factual reasons which would lead one skilled in the art to question objective truth of the statement of operability." *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

MPEP §2107.02 IV further states, a detailed explanation should be given for a utility rejection as to why the claimed invention has no specific and substantial asserted utility. Documentary evidence should be provided when possible. Otherwise the Examiner should specifically explain the scientific basis for his factual conclusions.

2. The Asserted Utility and the Examiner's Rejection

The instant application asserts a specific and substantial utility of the claimed invention. For example, it is asserted on page 6, lines 26-31, and page 58, lines 15-21, of the specification that the identification of Kir5.1 nucleic acids and polypeptides allows screening for modulators, activators, or inhibitors of potassium channels comprising a Kir5.1 subunit. These modulators are useful for treating conditions and diseases related to altered cell excitability in tissues where Kir5.1 is expressed, *e.g.*, hypertension, acute renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism,

hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency (*see, e.g.*, page 6, lines 26-31).

In the Final Office Action mailed June 16, 2003, the Examiner alleges that the instant specification fails to establish a specific and substantial asserted utility of the claimed invention. While conceding that the asserted utility of the Kir5.1 channel as an inward rectifier potassium channel to modulate cell excitability and membrane potential is credible, the Examiner argues that this asserted utility is not specific by questioning the validity of Example II on page 57 and Figure 1 for not having negative control cells expressing neither Kir5.1 nor Kir4.1. The Examiner further states that "this asserted utility...is not specific because such assays [as shown in Example II] can be performed with any polypeptide" (bridging paragraph between pages 4 and 5 of the Final Office Action). In the same paragraph, the Examiner goes on to say that "since the skilled artisan would not readily use the claimed polypeptide to form a heteromeric potassium channel because the protein has not shown to have an increased current magnitude compared to control, the asserted utility is not substantial."

Similarly, the Examiner argues in the Final Office Action of June 16, 2003, that the asserted utility of using Kir5.1 channel as a target for treating diseases and conditions caused by altered neuronal and cell excitability is credible, but not specific or substantial, because "[t]he specification discloses nothing about the normal levels of expression of the [Kir5.1] polynucleotide" or "the disorders or conditions associated with the Kir5.1 gene, either normal or mutated/deleted/translocated," and that without significant further experimentation to identify such disease or condition involving altered Kir5.1 gene, the asserted utility is not presented in a mature form for ready usage in a real world sense. See the bridging paragraph between pages 5 and 6 of the Final Office Action.

In the Advisory Action mailed September 11, 2003, the rejection for lack of utility is maintained. The Examiner again questions the validity of the results of

Example II as presented in Figure 1, expressing doubts about the interpretation of the experiment results without control cells expressing Kir4.1 only (first paragraph on page 2 of the Advisory Action). The Examiner further contends, in response to Appellant's communication with the PTO filed August 14, 2003, that the present case is not analogous to Example 8 of the Revised Interim Utility Guidelines Training Material, because "the structure and function of the [Kir5.1] nucleic acid molecule of the instant application is not known" and the invention therefore has no credible, specific, and substantial asserted utility or a well established utility (third paragraph on page 2 of the Advisory Action).

3. The Claimed Kir5.1 Polynucleotides Are Useful for Screening of Compounds for Treating Conditions and Disorders Related to Cell Excitability

As described in the present application, the present inventors cloned, for the first time, the human polynucleotide sequence encoding Kir5.1, an alpha subunit of an inward rectifier potassium channel (*e.g.*, page 6, lines 20-24, of the specification). The inventors also identified the amino acid sequence of human Kir5.1 and determined the tissue-specific expression pattern of Kir5.1 at the mRNA level (*e.g.*, Examples I and III). Furthermore, the inventors recombinantly expressed Kir5.1 and characterized the electrophysiological properties of the Kir5.1 channels (*e.g.*, Example II and Figure 1).

Because the Kir family of inward rectifier potassium channels is known to be involved in regulating potassium flow across cell membrane and therefore regulating cell resting potential and excitability (*e.g.*, page 2, line 25, to page 3, line 3, of the specification and references cited therein), one of skill in the art would expect a Kir5.1 potassium channel to play an important role in the proper physiological function of the tissues where it is specifically expressed, *e.g.*, in the kidney, thyroid, pancreas, and salivary gland (Example III on page 58). Thus, compounds capable of modulating the activity of a Kir5.1 potassium channel can be used for treating conditions and disorders in these tissues that are caused by abnormal potassium influx, such as hypertension, acute

renal failure, chronic renal failure, diabetes insipidus, diabetic nephropathy, hypothyroidism, hyperthyroidism, goiter, hypoparathyroidism, hyperparathyroidism, pancreatic insufficiency, diabetes, cystic fibrosis, sialorrhea, and salivary insufficiency (*e.g.*, page 6, lines 26-31).

The present application provides nucleotide sequences of human Kir5.1, methods of assaying Kir5.1 channel function, and methods of assaying for compounds increase or decrease ion flux of the Kir5.1 potassium channels. A skilled artisan, after reading the present application, would therefore be able to routinely identify modulators of the Kir5.1 channels and determine if a candidate compound can affect the physiology of tissues where Kir5.1 is expressed by altering Kir5.1 potassium channel activity.

Appellant thus contends that the asserted utility for the present invention is one supported by the general knowledge in the relevant field and a person of ordinary skill in the art would find such utility credible.

4. The Asserted Utility is Specific, Substantial, and Credible

Appellant maintains that the disclosure of human Kir5.1 polynucleotide and amino acid sequences for inward rectifier potassium channels expressed in certain tissues and the electrophysiological characterization of the Kir5.1 channels, combined with the methods disclosed in the specification and the level of skill in the art, is sufficient to establish a credible specific and substantial utility under the definitions provided by the MPEP.

Specific Utility

Appellant asserts that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP §§2107.01 and 2107.02. In the present application, Appellant

identifies the nucleic acid and amino acid sequences of human Kir5.1, demonstrates the expression pattern of Kir5.1, teaches the recombinant expression of Kir5.1, and illustrates the electrophysiological characteristics of the Kir5.1 channels. Appellant further discloses a "disease condition" (*i.e.*, disorders named on page 6, lines 28-31, of the specification including hypertension, renal failure, and the like) that correlates with a "biological activity" (*i.e.*, the opening and closing of a Kir5.1 channel). The application provides methods for identifying compounds capable of modulating the Kir5.1 channel activity. These compounds can therefore be used, *e.g.*, for treating conditions and disorders related to abnormal potassium influx in certain tissue types where Kir5.1 is expressed. Appellant thus submits that the present invention has a specific utility, namely that Kir5.1 channels can mediate potassium influx in, *e.g.*, kidney, thyroid gland, or pancreas, which is clearly specific for the claimed Kir5.1 channels and not any ion channels.

The Examiner's position that this asserted utility is not specific is unattainable. As described above, the Examiner contends that the asserted utility lacks specificity because "the assays [as shown in Example II] can be performed with any polypeptide" (bridging paragraph between pages 4 and 5 of the Final Office Action mailed June 16, 2003). Appellant cannot agree with the Examiner's reasoning on this point. What the Examiner has stated is merely an irrelevant truth, because the asserted utility of the Kir5.1 channel relies not on the performing of the assays *per se*, but rather on the results of the assays confirming the functional characteristics of an inward rectifier potassium channel. Such results cannot be obtained from assaying any polypeptide or even any ion channel.

The Examiner further contends that the asserted utility of the present invention is not specific and/or substantial because the Examiner remains doubtful of the results of Example II as shown in Figure 1. Appellant believes that in questioning the validity of Example II and interpretation of its results, the Examiner is in fact questioning

the credibility of the asserted utility. This aspect of the asserted utility and Example II will be addressed below.

Substantial Utility

Appellant also asserts that the present invention has a substantial or "real-world" use. This invention provides human Kir5.1 channel polynucleotide and polypeptide sequences. The application also demonstrates that the Kir5.1 channels can modulate potassium influx in cells where Kir5.1 is recombinantly expressed, and therefore asserts that the Kir5.1 channels can function in the same manner in tissue such as kidney, thyroid gland, and pancreas where Kir5.1 is highly expressed. The application further teaches how to identify agonists and antagonists of the Kir5.1 channels. For example, on pages 40-42 of the specification, assays are described that can be used to test for inhibitors and activators of the Kir5.1 channels, *e.g.*, assays that involve measuring current, measuring membrane potential, measuring ion flux, or measuring patch-clamp electrophysiology. The present invention therefore has a real-world use in modulating the physiology of tissues in which Kir5.1 is expressed, as well as in the identification of compounds that modulate Kir5.1 channels and thus can be useful as therapeutic agents for treating diseases or conditions related to altered potassium influx, particularly in tissues such as kidney, thyroid gland, and pancreas.

The Examiner argues that the asserted utility is not substantial, reasoning that "the skilled artisan would not readily use the claimed polypeptide to form a heteromeric potassium channel because the protein has not shown to have an increased current magnitude compared to control" (bridging paragraph between pages 4 and 5 of the Final Office Action dated June 16, 2003). The Examiner further states that because "[t]he specification discloses nothing about the normal levels of expression of the [Kir5.1] polynucleotide" or "the disorders or conditions associated with the Kir5.1 gene, either normal or mutated/deleted/translocated," and that without significant further experimentation to identify such disease or condition involving altered Kir5.1 gene, the

asserted utility is not presented in a mature form for ready usage in a real world sense (the bridging paragraph between pages 5 and 6 of the Final Office Action). Appellant respectfully disagree with the Examiner.

First of all, a skill artisan can, upon reading the present disclosure, readily use the Kir5.1 polypeptide to form a heteromeric potassium channel. This has been done and is evidenced by Example II and Figure 1. Example II is intended to demonstrate the difference in potassium influx profile between a Kir5.1 homomeric channel and a Kir5.1-Kir4.1 heteromeric channel. Thus, no absolute negative control of cells expressing neither Kir5.1 nor Kir4.1 is necessary. For the same reason, a control sample of cells expressing only Kir4.1 is not needed either, as the experiment is not designed to study the characteristics of Kir4.1 homomeric channels. Secondly, the specification does disclose the normal expression levels of Kir5.1 polynucleotide in various tissues, see Example III on page 58. Thirdly, the specification does name a large number of diseases and conditions (such as hypertension and renal failure) that can be treated by modulators of Kir5.1 channels (*see, e.g.*, page 58, lines 18-21), which clearly provides a real world use of the modulators and thus the Kir5.1 nucleic acid or polypeptide. The Examiner's reasoning behind the utility rejection ignores the practical, real world uses asserted by the present application, apparently because the Examiner does not believe these asserted uses, even though the rejection is not phrased to question the credibility of the asserted utility.

Credible Utility

Finally, Appellant contends that the asserted utility of the present invention is credible, *i.e.*, would be believable to one of skill in the art. Appellant submits that an ordinarily skilled artisan, after reading this application, would know (a) how to identify the Kir5.1 channels; (b) how to identify modulators of the Kir5.1 channels; and (c) how to use these modulators so identified to modulate potassium flux in cells where Kir5.1 is expressed. Because of the pre-existing knowledge of the Kir family

potassium channels and the high expression level of Kir5.1 in organs such as kidney, thyroid gland, and pancreas, one skilled in the art would believe that the identification of a new potassium channel Kir5.1 in these organs is useful for developing new therapeutics for treating disorders caused by abnormal potassium influx in the cells of these tissue types.

Although the Examiner states that the asserted utility is credible but not specific or substantial, Appellant believes that the Examiner's reasoning for the utility rejection in fact focuses on the credibility issue of the asserted utility. Thus, Appellant will further address the issue of credible asserted utility in the following sections.

5. The Examiner's Disbelief of the Asserted Utility is without Objective Reasons

Despite the concession that a credible utility has been asserted in the specification, the Examiner maintains the utility rejection apparently based on personal disbelief of the asserted utility rather than any credible scientific evidence. For example, the Examiner states in the June 16, 2003, Final Office Action that "the skilled artisan would not readily use the claimed polypeptide to form a heteromeric potassium channel because the [Kir5.1 channel] has not been shown to have an increased current magnitude compared to control" (the bridging paragraph between pages 4 and 5 of the Final Office Action). In fact, Appellant has asserted throughout the specification that the Kir5.1 channel is an inward rectifier potassium channel, *i.e.*, would show "an increased current magnitude compared to control." Appellant has further shown in Example II and Figure 1 that Kir5.1 and Kir4.1 can form a functional heteromeric potassium channel. Yet the Examiner questions the credibility of these assertions by Appellant while providing no scientific evidence or reasoning to support her doubts.

The Examiner further states that the specification "does not disclose disorders or conditions associated with the Kir5.1 gene" (bottom of page 5 of the Final Office Action), despite the fact Appellant has repeatedly asserted that modulators of the Kir5.1 channel can be used to treat diseases and conditions (such as hypertension, renal

failure, etc.) occurring in, *e.g.*, kidney, thyroid gland, and pancreas, where Kir5.1 gene is highly expressed (*see, e.g.*, page 6, lines 28-31, and page 58, lines 18-21, of the specification). As discussed above, based on the general knowledge of the Kir family of potassium channels and expression pattern of Kir5.1, one of skill in the art would reasonably expect Kir5.1 to be a therapeutic target for effective treatment of conditions or disorders caused by abnormal potassium influx in relevant tissues, regardless whether Kir5.1 is the direct cause of such conditions or disorders. On the other hand, the Examiner again questions Appellant's asserted utility but provides no scientific evidence to support her disbelief.

Similarly, in the Advisory Action mailed September 11, 2003, the Examiner contends that the present case is not factually analogous to Example 8 of the Revised Interim Utility Guidelines Training Material, because "the structure and function of the [Kir5.1] nucleic acid molecule of the instant application is not known" (third paragraph on page 2 of the Advisory Action). This statement clearly shows that the Examiner does not believe Appellant's asserted structure and function of the Kir5.1 gene: encoding a subunit of an inward rectifier potassium channel. Yet again, no reasoning based on objective evidence is given by the Examiner to justify such disbelief.

Raising a rejection for lack of utility in such a manner is inconsistent with the proper practice described in the MPEP, which places the initial burden on the Examiner, not Appellant, to provide evidence to support a factual conclusion of the credibility of an asserted utility. In fact, MPEP §2107.02 III.B. specifically cautions Office personnel that, once an assertion of a particular utility is made, "that assertion cannot simply be dismissed ..... as 'wrong,' even when there may be reason to believe the assertion is not entirely accurate." Instead, the Examiner must provide an explanation setting forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied upon in reaching the conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV.

The Examiner has provided none of the above. The pending claims are rejected for lack of utility simply because the Examiner does not believe the specific and substantial utility asserted by Appellant. Appellant respectfully submits that the Examiner's disbelief, without more, cannot properly sustain the rejection.

6. Finding Sufficient Utility in the Present Application is Consistent with the Policy of Encouraging Early Disclosure

Our patent law places much emphasis on encouraging early disclosure of inventions. This is a particularly relevant policy consideration in case law involving the utility standard under 35 U.S.C. §101. In *Brenner v. Manson*, 148 USPQ 689 (US Sup. Ct. 1966), for instance, the Supreme Court ruled that a process to produce a compound may be patented only if the compound has "substantial utility," "specific benefit ... in currently available form." Whether granting patent protection to the discovery of a new process or compound with a yet unknown practical utility would encourage prompt disclosure of inventions was one factor the Court carefully considered and to a significant extent relied upon in reaching the landmark decision. 148 USPQ at 695.

In *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), the CCPA was confronted with a situation where the claimed compound, 16-phenoxy-substituted prostaglandin (PG), was shown to have some pharmacological activity, *i.e.*, causing changes in blood pressure in the rat blood pressure (BP) test and stimulation of smooth muscles in the gerbil colon smooth muscle stimulation (GC-SMS) test, yet no specific therapeutic use for the compound was established. In deciding the question of utility, the CCPA stated:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illness and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many as compounds as possible, we conclude that adequate proof of any such activity constitute a showing of practical utility.

Nelson, 206 USPQ at 883. The present case is analogous to *Nelson*. Because abnormal ion influx can interfere with the normal physiological functions of organs and tissues, compounds capable of modulating ion channels, such as the Kir5.1 channels, are useful as therapeutic agents for treating these conditions. Assays for screening of ion channel modulators is thus beneficial to the public and the disclosure of how to perform these assays should be encouraged. The present application provides just this kind of disclosure. To hold that the present invention lacks sufficient utility under 35 U.S.C. §101 to warrant patent protection would be inconsistent with the underlying policy of case law and create a strong disincentive for researchers to disclose their inventions of this type.

7. Summary

In light of the foregoing discussion, Appellant believes that the utility rejection under 35 U.S.C. §101 is improper and should be withdrawn.

B. The Rejection for Inadequate Enablement Based on Utility Is Improper

The Examiner has also rejected claims 1-4, 6, and 7 as not being enabled, on the ground that the claimed invention is not supported by either a credible specific and substantial asserted utility or a well-established utility. As discussed above, the claimed invention has a credible asserted utility, which is also specific and substantial under the examination guideline set forth in the MPEP. Appellant therefore believes that the utility-based enablement rejection under 35 U.S.C. §112, first paragraph, is improper and should be withdrawn.

C. The Rejection for Indefiniteness Is Improper

The Examiner has further rejected claims 1-4, 6, and 7 under 35 U.S.C. §112, second paragraph, alleging failure to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner contends that the recitation of hybridization conditions does not provide an unambiguous

definition of the hybridization stringency and therefore does not properly define the metes and bounds of the claimed nucleic acids.

As will be discussed in detail below, pending claims define the Kir5.1 nucleic acid of the present invention by reciting, among other things, hybridization conditions, and fully comply with the statutory requirement under 35 U.S.C. §112, second paragraph. Appellant thus submits that the indefiniteness rejection is improper and should be withdrawn.

1. Standard for Definiteness

According to the MPEP §2173, to satisfy the statutory requirement under 35 U.S.C. §112, second paragraph, claims must particularly point out and distinctly claim the subject matter of the invention. The essential inquiry pertaining to the definiteness requirement is whether a claim sets out and circumscribes a particular subject matter with a reasonable degree of clarity and particularity so as to appraise one of skill in the art of the claim scope. An indefiniteness rejection is appropriate when a person of ordinary skill in the art could not interpret the metes and bounds of the claim. MPEP §2173.02. The same section of the MPEP further states that definiteness of a claims must considered as a whole and in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

2. Recited Hybridization Conditions and the Examiner's Rejection

Claim 1 of the present application is drawn to an isolated nucleic acid encoding a polypeptide monomer comprising an alpha subunit of a potassium channel. This polypeptide monomer has the following attributes: (i) it forms, with at least one additional Kir alpha subunit, a potassium channel having the characteristic of inward rectification; and (ii) it is encoded by a nucleic acid that selectively hybridizes under

highly stringent hybridization conditions to a nucleotide sequence of SEQ ID NO:2, wherein the stringent conditions comprise incubation at 42°C in a solution comprising 50% formamide, 5 x SSC, and 1% SDS or an incubation at 65°C in a solution comprising 5 x SSC and 1% SDS at 65°C with a wash in 0.2 x SSC and 0.1% SDS.

In the final Office Action mailed June 16, 2003, the Examiner rejects claims 1-4, 6, and 7 for alleged indefiniteness, asserting that the hybridization conditions are indefinite unless the claim recites the hybridization conditions as "consisting of" "**A** X SSC and **B** % SDS at **C** °C" (bridging paragraph between pages 7 and 8 of the final Office Action).

Despite Appellant's arguments and submission of supporting references, the Examiner continues to reject the claims in the Advisory Action dated September 11, 2003, contending that the "comprising" language would allow additional ingredients that may lower hybridization stringency and therefore allow the claims to cover non-Kir5.1 polynucleotide variants (the bridging paragraph between pages 2 and 3 of the Advisory Action).

3. Recited Hybridization Conditions Allow One of Skill in the Art to Determine the Metes and Bounds of the Claimed Invention

Appellant contends that the hybridization conditions as recited in claim 1 would allow one of skill in the art to properly determine the metes and bounds of the claimed invention. To support this position, two references, excerpts of Roche Applied Science product manual and *Molecular Cloning: A Laboratory Manual*, were submitted as Exhibits A and B, respectively, long with Appellant's communication to the PTO filed August 14, 2003.

In particular, the Roche manual describes the main factors that can affect nucleic acid hybridization stringency: temperature, pH, monovalent cations (such as Na^+ in SSC and SDS), and formamide. Among these factors, the manual indicates that pH has little effect on hybridization when in the range of 5-9, even though higher pH can

lead to more stringent conditions. The manual further states that Na^+ concentrations above 0.4 M in a hybridization solution have only very slight effect on hybridization stringency (the left column on page 33 and page 34 of the Roche manual).

Claim 1 recites specific hybridization and wash temperatures. Claim 1 also recites a specific concentration of formamide. Claim 1 further recites a hybridization solution comprising a 5 x SSC and 1% SDS. Since 5 x SSC contains 0.75 M NaCl and 0.075 M tri-sodium citrate, this hybridization solution has a Na^+ concentration clearly above 0.4 M. Therefore, even if additional monovalent cations may be included in the hybridization solution, the level of stringency will not be significantly effected.

Given the level of technical sophistication in the field of biochemistry and molecular genetics, one of skill in the art would be able to readily determine if a given polynucleotide sequence could selectively hybridize to SEQ ID NO:2 under the conditions recited in claim 1. Thus, the recited hybridization conditions allow an artisan to determine the metes and bounds of the claimed invention with clarity and particularity.

4. Claim 1 as a Whole Provides Further Clarity and Precision in Defining the Invention

Besides reciting the hybridization conditions, which provides a structural limitation of the claimed Kir5.1 nucleic acid, claim 1 also recites a functional limitation of the claimed Kir5.1 nucleic acid: the nucleic acid encodes a polypeptide monomer comprising an alpha subunit of a potassium channel. This polypeptide monomer forms, with at least one additional Kir alpha subunit, a potassium channel having the characteristic of inward rectification.

The present application describes assay methods for assessing the functionality of an inward rectifier potassium channel (*see, e.g.*, Example II), such that one of skill in the art would be able to examine the functional characteristics of a polypeptide and determine whether the coding polynucleotide sequence for this polypeptide is within the claim scope in the functional aspect. The art in the field of

electrophysiology is highly advanced and various methods for functional verification of an inward rectifier potassium channel are known to those skilled in the art. Thus, the claim language reciting functionality of the claimed Kir5.1 nucleic acid would further allow a skilled artisan in the relevant field to determine the metes and bounds of the claimed invention, with additional clarity and precision beyond that afforded by the structural aspect of the invention as defined by the hybridization conditions.

When considered as a whole, even if the Examiner were correct in that the recited hybridization conditions would lead to some ambiguity of the claim scope, the functional language of claim 1 would allow one of skill in the art to determine the claim scope with sufficient certainty, as those non-Kir5.1 polynucleotide variants the Examiner is concerned might be brought in by the hybridization language could be readily excluded from the claimed invention based on the functional requirement.

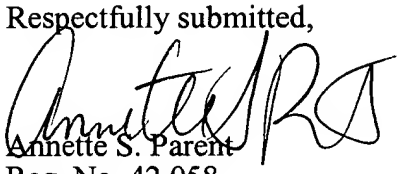
5. Summary

Appellant believes that the recited hybridization conditions in claim 1 properly define the metes and bounds of the claimed invention to a person of skill in the art, as required by 35 U.S.C. §112, second paragraph, particularly when the claim is considered as a whole and in light of the disclosure of the present application, the state of the art, and the claim interpretation by a person of ordinary skill in the art at the time of the invention. Accordingly, Appellant respectfully submits that the indefiniteness rejection is improper and should be withdrawn.

VIII. CONCLUSION

In view of the foregoing, Appellant believes all claims now pending in this Application are in condition for allowance.

Respectfully submitted,



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APPENDIX: PENDING CLAIMS

1. (Previously presented) An isolated nucleic acid encoding a polypeptide monomer comprising an alpha subunit of a potassium channel, the polypeptide monomer:

(i) forming, with at least one additional Kir alpha subunit, a potassium channel having the characteristic of inward rectification; and

(ii) encoded by a nucleic acid that selectively hybridizes under highly stringent hybridization conditions to a nucleotide sequence of SEQ ID NO:2, wherein the stringent conditions comprise incubation at 42°C in a solution comprising 50% formamide, 5 x SSC, and 1% SDS or an incubation at 65°C in a solution comprising 5 x SSC and 1% SDS at 65°C with a wash in 0.2 x SSC and 0.1% SDS.

2. (Original) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes human Kir5.1.

3. (Original) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes SEQ ID NO:1.

4. (Original) The isolated nucleic acid sequence of claim 1, wherein the nucleic acid has a nucleotide sequence of SEQ ID NO:2.

5. (Canceled)

6. (Previously presented) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide monomer having a molecular weight of about between 38 kDa to 48 kDa, wherein the molecular weight is predicted based on amino acid sequence.

7. (Original) The isolated nucleic acid of claim 1, wherein the polypeptide monomer comprises an alpha subunit of a heteromeric inward rectifier potassium channel.

8-35. (Canceled)